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Research Article

Bronchodilator response in preschool asthma: a predictor of future spirometry abnormalities

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Abstract

Introduction

Altered airway obstruction reversibility has been identified in some pediatric asthma phenotypes that are associated with a worse clinical course. The aim of this study was to evaluate if bronchodilator response (BDR) in asthmatic children under six years old was associated with spirometry findings at school age.

Methods

Prospective study conducted between 2018 and 2023 with persistent asthma preschoolers who initially underwent pre- and post-bronchodilator spirometry and one after 3 years. The best preschool BDR cut-off points for predicting abnormal spirometry, small airway dysfunction (SAD), and school-age BDR were measured.

Results

89 patients with a mean age of 5.3 and 8.3 years in their first and second evaluation were studied. 57.3% were male. In first evaluation FEV 0.75/FVC BDR ≥ 8.9% of the baseline, FEV 0.75/FVC BDR ≥ 7.6% of predicted value and FEV 0.75 BDR ≥ 9.3% of the baseline had the best AUC to predict abnormal spirometry (0.76, 0.74 and 0.72 respectively) or SAD at school age (0.76, 0.74 and 0.73 respectively). FEV1/FVC BDR ≥ 7.3% of baseline (LR+ 4.1) was the best parameter to increase the probability of abnormal spirometry and FEV 0.5% BDR of the baseline ≥ 22.6% and ≥ 23.4% best for SAD and BDR at school age (LR+ 9.5 and 4.8 respectively).

Conclusion

The findings of this study indicate that some parameters of the BDR between 3 and 5 years of age are useful for predicting spirometry abnormalities at school age.

Keywords: Asthma; Preschoolers; Schoolchildren; Spirometry; Bronchodilator response

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Introduction

Airway lability is a characteristic feature of children with asthma. As such, bronchodilator reversibility testing is routinely performed in the clinical setting to confirm the diagnosis of asthma and quantify the asthma control [1]. Bronchodilator reversibility has been identified in phenotypic subgroups of children with asthma [2] and may contribute to differing clinical outcomes and disease trajectories [3]. In the Childhood Asthma Management Program (CAMP), a small subset of children with consistent improvement in forced expiratory volume in the first second (FEV1) of 12% or greater after bronchodilator administration had more nocturnal symptoms, prednisone bursts, missed days at school and hospitalizations [4]. Other studies have likewise identified greater bronchodilator reversibility in children with difficult control or severe asthma who also have greater symptoms despite inhales corticosteroids treatment [5,6]. A positive reversibility test has recently been recommended for the diagnosis of asthma, which considers a 12% improvement in FEV1 in children and young people (5 to 16 years of age) who have previously performed obstructive spirometry with FEV1/FVC ratio less than 70% [7]. However, the latest ATS/ERS consensus on lung function recommends not confusing the bronchodilator response with the "reversibility" of airflow obstruction, which is a qualitative term that reflects the normalization of FEV1/FVC and recommends considering the bronchodilator response (BDR) in children and adults when there is a 10% increase for FEV1 and/or FVC after bronchodilator [8].

The evidence of spirometry BDR in preschool asthma is scant and limited to a few case control studies in which they have been found significant differences between the BDR measured in healthy preschool children compared with children with asthma or recurrent wheeze [9]. We are unaware of information on the asthmatic BDR in preschool children and its relationship with lung function at school age. The purpose of this study was to assess whether a significant BDR in asthmatic children under six years of age can discriminate between school-age asthmatics with normal or abnormal spirometry, with or without small airway dysfunction and with or without BDR at school-age.

Patients and Method

This non-randomized prospective study was conducted at the pediatric pulmonology laboratory of Clínica Las Condes, Santiago, Chile, between August 2018 and September 2023, in a cohort of children with persistent asthma followed from 3 to 8 years old, managed in our department that pulmonary function tests had been performed.

The inclusion criteria were a confirmed diagnosis of persistent asthma by a pediatric pulmonologist, according to the recommendations of the Global Initiative for Asthma [1]. Children with other chronic respiratory diseases, cardiopathies, prematurity (<37 weeks of gestation), and immunodeficiencies were excluded.

At the first evaluation (2018 to 2020), persistent asthmatic preschoolers aged 3 to 5 years who performed pre- and post- bronchodilator spirometry were enrolled. Thereafter they were monitored by their treating physician, who indicated and/or adjusted the treatment, following GINA recommendations [1].

After 3 years (2021–2023), it was confirmed that the patients still had persistent asthma according to GINA's criteria and a new pre- and post-bronchodilator spirometry was performed. In both evaluations, post-bronchodilator spirometry was performed with 400 µg albuterol. FEV1 (L), FVC (L), FEV1/FVC ratio (%), FEV 0.75 (L), FEV 0.5 (L), FEV 0.75/CVF ratio (%) and FEF 25–75 (L) was measured. The spirometry was performed according to ATS/ERS guidelines [10-12], using the Vyaire Vyntus model v-176430 (Mettawa, IL). On children ≥ 6 years old abnormal spirometry was defined when the FEV1 and/or FEV1/FVC and/or FVC values were below the lower limit of normality (LLN) according to Quanjer predictive values [13]. On children under 6 years old, FEV 0.75 and/or FEV 0.75/FVC < LLN were also considered for this definition. It was considered a significant BDR an increase of 10% for FEV1 and/or FVC after albuterol MDI 400 ug administered with a spacer device [7]. SAD was defined when the FEF 25-75 was below LLN according to the Quanjer predictive values [13].

BDR was evaluated in FEV1, FEV 0.75, FEV 0.5, FEF 25-75, FEV1/FVC and FEV 0.75/FVC. The changes in the BDR for each parameter were calculated by the following formulas:

(post-bronchodilator value – pre-bronchodilator value) x 100 / predicted value

(post-bronchodilator value – pre-bronchodilator value) x 100 / pre- bronchodilator value

Because the Global Lung Function International (GLI) does not have FEV 0.5 predictive values for our population, the BDR for this parameter was calculated with respect to the pre-bronchodilator value.

Written consent was obtained from the parents/guardians of children who agreed to participate after receiving information about the study. The study was approved by the ethics committee of the institution.

The Skin prick test (SPT) at preschool age was carried out using the most common allergens in our city [14], administered on the forearms, as well as positive (histamine) and negative (solvent) controls. The SPT was performed by only one technician, who was blind to the clinical characteristics of the child's asthma and was considered as positive when in one or more allergens there was a reaction greater than 3 mm.

Statistical analysis

The best cut-off points of preschool BDR to detect altered school spirometry, SAD or BDR were calculated using the area under the curve (AUC). The sample size used to measure diagnostic tests was calculated based on LR+ (positive likelihood ratio) = sensitivity / 1- specificity, considering the sensitivity and specificity with the best cut-off points for the prevalence of abnormal spirometry, SAD or BDR in schoolchildren. Sample size: A minimum of 85 patients were needed to detect abnormal spirometry, SAD o BDR at school-age. For all calculations, an α error of 5%, a β error of 20%, and a percentage of loss at follow-up not greater than 10% was considered. Statistical significance was established at a p-value of less than 0.05. For the statistical analysis, SPSS® v17.0 (IBM, Armonk, NY) software was used.

Results

89 preschoolers who performed correctly pre- and post-bronchodilator spirometry were included. 57.3% of theme were male. The age distribution at first evaluation was: 4.5% were 3 years old, 30.3% were 4 years old and 65.2% were 5 years old. 76.4% received controller therapy. After three years follow-up, all enrolled children were able to perform spirometry. The distribution age of the second evaluation were 6 years (5.6%), 7 years (24.7%), and 8 years (69.7%). 80.9% received controller therapy (Table 1).

	At Preschool-age (≥ 3yr and < 6yr) (2018-2020)	At School-age (≥ 6yr and < 9yr) (2021-2023)
Age (years)	5.3 ± 0.9	8.3 ± 1.1
Weight (K)	20.6 ± 4	30.3 ± 5
Height (cm)	112.2 ± 7.6	130.5 ± 8
Abnormal spirometry (%)	28.1	21.3
Small Airway Dysfunction (%)	29.2	17.9
Bronchodilator response (%)	28	25.8
Controller Therapy : ICS only (%)	47.2	29.2
ICS + LABA (%)	23.6	49.4
LTRA (%)	5.6	2.3

Table 1: Clinical-demographic characteristics of the cohort of persistent asthmatics patients in the two evaluations (N=89).

Numbers are expressed in %, mean and standard deviation, ICS = Inhaled corticosteroids, LABA= Long-acting beta-agonist, LTRA= leukotriene receptor antagonists.

Spirometry parameter	Baseline $\bar{x} \pm SD$	Post-bronchodilator $\bar{x} \pm SD$	Δ%Pred $\bar{x} \pm SD$	Δ%Init $\bar{x} \pm SD$
Preschool-age				
FVC	1.4 ± 0.3	1.44 ± 0.3	2.9 ± 0.1	2.8 ± 0.1
FEV1	1.2 ± 0.2	1.27 ± 0.2	7 ± 0.1	7 ± 0.1
FEV0.75	1.08 ± 0.2	1.17 ± 0.2	9 ± 0.1	9 ± 0.1
FEV0.5	0.91 ± 0.3	1 ± 0.2	NA	11 ± 0.1
FEF25-75	1.2 ± 0.4	1.5 ± 0.4	17 ± 0.2	27 ± 0.3
FEV1 / FVC	85.4 ± 12	87.8 ± 11	3 ± 0.1	3 ± 0.1
FEV0.75/ FVC	77 ± 8	82 ± 7.3	5 ± 0.1	6 ± 0.1
School-age				
FVC	2.2 ± 0.4	2.2 ± 0.4	0 ± 0.1	0.9 ± 0.2
FEV1	1.8 ± 0.4	1.9 ± 0.4	7 ± 0.1	7 ± 0.1

FEF25-75	1.7 ± 0.5	2.1 ± 0.6	18 ± 0.2	26 ± 0.2
FEV1 / FVC	81.9 ± 13	85.9 ± 13	4 ± 0.1	5 ± 0.1

Table 2: Means, standard deviation, and percentage change from baseline and predicted value at preschool and school-age (N=89).

Δ%Init: percentage change reported to initial value, NA: not applicable for our population, FEV1, FEV 0.75 and FEV 0.5 : forced expiratory volume in L during 1, 0.75 and 0,5 seconds of forced vital capacity, FEF25-75 : forced expiratory flow at 25–75% of the forced vital capacity in Ls, predicted: values according to Quanjer et al. (13)

The severity of the asthma was 24.4% mild persistent, 57.3% moderate persistent and 18.3% severe persistent in both assessments. The mean ± SD pre- and post-bronchodilator with their percentages of change with respect to the baseline and predicted values are shown in (Table 2).

All preschool BDR parameters analyzed exceeded the non-discrimination value (AUC = 0.5) to detect abnormal spirometry, SAD or BDR at school age. Some of these preschool BDR parameters had acceptable diagnostic accuracy (AUC>0.7) to detect abnormal spirometry and in decreasing order were: FEV 0.75/FVC % change of baseline, FEV 0.75/FVC % change of predicted, FEV 0.75 % change of baseline, FEV1/FVC % change of baseline, FEV1/FVC % change of predicted, FEV1 % change of baseline and FEV1 % change of predicted (Table 3). The preschool BDR parameters that had the best capacity to detect SAD at school age and these were in decreasing order: FEV 0.75/FVC % baseline, FEV 0.75/FVC % change of predicted, FEV 0.75 % change of baseline and FEV1 % change of baseline (table 4). Two preschool BDR parameters were found with the highest LR+ for abnormal spirometry: FEV1/FVC ≥ 7.3% change from baseline, FEV 0.5 ≥ 18.2% change from baseline (table 3). According to these results if the BDR exceeds these cut-off points, the prevalence (pretest probability) of abnormal spirometry (21%) would rise to 53% and 51% respectively. FEV 0.5% change of Baseline ≥ 22.6%, FEV 0.75% change from predicted ≥18% and FEV1/FVC% change from baseline value ≥7.6%, had the highest LR+ to predict SAD (table 5), and according to these results, if a preschooler having a BDR higher than these cutoffs, the prevalence (pretest probability) of SAD (17.9%) rises to 68%, 51% and 42% respectively.

FEV 0.5% change from baseline ≥23.4% and FEV 0.75/FVC % change from baseline ≥12.1% were two BDR parameters that had the highest LR+ for BDR at school age and according to these results, if the pre-school BDR exceeds these cut-off points, the prevalence (25.8%) of school BDR (pretest probability) would increase to 62.8% and 56.5%, respectively (Table 4).

Except for the BDR in the FEF 25-75, most of the parameters analyzed had a high negative predictive value (85-90%) to rule out abnormal spirometry or SAD at school age, this means that the preschoolers with values of BDR below the cut-off points reported in this study have a low probability of abnormal spirometry or SAD at school age (Tables 3 & 5).

The cut-off points obtained in the subgroup of preschoolers with a positive SPT were analyzed. Some parameters with LR+ increase the probability of abnormal spirometry at school age in this group: FEV1/FVC BDR ≥ 7.3% compared to baseline (LR+ = 5.5), FEV 0.5 BDR ≥ 18.2% with respect to baseline (LR+ = 4.1) and FEV 0.75/FVC ≥ 8.9% with respect to baseline (LR+= 3.7). In this subgroup, the prevalence (pre-test probability) of abnormal spirometry, SAD or BDR was 23.4%, 17% and 19.1%, respectively, and after applying the BDR cut-off points, the abnormal spirometry post-test probabilities rises to 62.7%, 55.6%, 53% respectively. No change in the post-test probability for SAD or BDR at school age was found in the group of patients with a positive SPT (data not shown).

Discussion

In this study we found that a significant group of preschoolers with persistent asthma have abnormal spirometry, evidence of SAD, and BDR. This is consistent with the fact that most of the patients had moderate to severe asthma.

In this group of persistent asthmatics, it was possible to demonstrate that some BDR parameters between 3 and 5 years of age can increase the probability of having abnormal spirometry or small airway dysfunction or BDR after three years of follow-up.

FEV 0.75/FVC % change from baseline or predicted were the two BDR parameters that achieved better AUC with moderate values to predict abnormal spirometry or SAD at school age and higher than the parameters traditionally used to measure preschool BDR (FEV1, FEV 0.75 and FEV 0.5). This is a new finding, but it could be in line with Néve et al., who previously reported in preschool children that FEV 0.75/FVC < LLN was the spirometry parameter that was best associated with recurrent wheezing (OR=9.7) or uncontrolled recurrent wheezing (OR=2.5) [15].

FEV 0.75 BDR ≥ 9.3% of baseline was another of the preschool parameters with moderate AUC to detect abnormal spirometry or SAD. Also, this parameter had a high LR+ to increase the post-test probability of SAD in schoolchildren. Together with FEV 0.75/FVC BDR could be a useful tool for monitoring and predict pulmonary function outcome in children under six years old. Both parameters are related to peripheral airway function, FEV 0.75 reflects limited expiratory flows. This could explain the results observed in this study. Three previous case-control studies conducted in preschool children in the same age range that our cohort and with the same dose of bronchodilator (400 µg albuterol) showed that a BDR in FEV 0.75 > 8.5%, >11% and > 14% were the best cut-off points to discriminate between asthma and healthy children and they confirm the usefulness of this parameter [16-18].

FEV 0.5 BDR ≥ 22.6% of baseline was the preschool bronchodilator response parameter with the highest LR+ to increase the probability of SAD three years later. FEV 0.5 BDR ≥ 18.2% and ≥ 23.4% also had a good LR+ to increase the probability of abnormal spirometry and BDR respectively. Burity et al. recommended BDR cut-off points for percent predicted FEV 0.5 ≥ 16% and for baseline FEV 0.5 ≥ 20% (16). Linares et al. conducted a study in preschoolers with and without asthma and found a cut-off point of FEV 0.5 BDR > 11% to discriminate between the two groups [19]. Other studies carried out in preschooler's asthmatic with a moderate-severe asthma percentage similar to our study, reported FEV 0.5 BDR > 15% in moderate asthma and 21% in severe asthma [20]. Elevated BDR values can be observed in patients with moderate to severe asthma and may be associated with having altered lung function in the future.

In this study, the preschool FEV1 BDR (baseline and predicted) increases the probability of having abnormal spirometry and SAD at school age. The cut-off points found (≥ 9.3% and ≥ 10.3%) are like those reported to discriminate between healthy and recurrent wheezer children (≥ 9%) to detect controlled asthma (≥ 10%) and predict the response to treatment with inhaled corticosteroids in children with mild symptoms (≥ 9 %) or with normal lung function (≥ 10%) [21-24].

	Abnormal school spirometry at school-age							
Preschool BDR	Optimal Cut-off point	AUC (95% CI)	S (%) (95% CI)	E (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	LR+ (95% CI)	LR- (95% CI)
Δ%Pred FEV1	≥ 9.3	0.7 (0.5-0.8)	63.2 (41-81)	77.1 (66-85)	42.9 (27-61)	88.5 (78-94)	2.8 (2.2-3.4)	0.5 (0.4-0.6)
Δ%Init FEV1	≥ 10.3%	0.7 (0.5-0.8)	63.2 (41-81)	78.6 (68-87)	44.4 (28-63)	88.7 (78-94)	2.9 (2.4-3.7)	0.5 (0.4-0.6)
Δ%Pred FEV0.75	≥ 12.8%	0.68 (0.5-0.8)	52.6 (32-73)	81.4 (71-89)	43.5 (26-63)	86.4 (76-93)	2.8 (2-3.9)	0.6 (0.5-0.7)
Δ%Init FEV0,75	≥ 9.3%	0.72 (0.6-0.9)	73.7 (51-88)	67.1 (55-77)	37.8 (24-54)	90.4 (79-96)	2.2 (1.9-2.5)	0.39 (0.3-0.6)
Δ%Init FEV0,5	≥ 18.2%	0.67 (0.5-0.8)	52.6 (32-73)	85.7 (76-92)	50 (30-70)	87 (77-93)	3.8 (2.5-5.3)	0.55 (0.4-0.7)
Δ%Pred FEF25-75	≥ 29.5%	0.51 (0.4-0.7)	36.8 (19-59)	78.6 (68-87)	31.8 (16-53)	82.1 (71-89)	1.7 (0.9-3.2)	0.8 (0.7-0.9)
Δ%Init FEF25-75	≥ 32.9%	0.59 (0.4-0.7)	52.6 (32-73)	71.4 (60-81)	33.3 (19-51)	84.8 (73-92)	1.8 (1.4-2.4)	0.6 (0.5-0.8)
Δ%Pred FEV1/FVC	≥ 6.2%	0,7 (0.5-0.8)	52.6 (32-73)	82.8 (72-90)	45.5 (27-65)	86.6 (76-93)	3.1 (2-4)	0.57 (0.5-0.7)
Δ%Init FEV1/FVC	≥ 7.3%	0.71 (0.6-0.9)	57.9 (36-77)	85.7 (76-92)	52.4 (32-72)	88.2 (78-94)	4.1 (2.9-5.6)	0.49 (0.3-0.6)
Δ%Pred FEV0,75/FVC	≥ 7.6%	0.74 (0.6-0.9)	57.9 (36-77)	80 (69-88)	44 (27-63)	88 (77-94)	2.9 (2.2-3.8)	0.52 (0.4-0.7)
Δ%Init FEV0,75/FVC	≥ 8.9%	0.76 (0.6-0.9)	63.2 (41-81)	81.4 (71-89)	48 (30-66)	89.1 (79-95)	3.4 (2.7-4.3)	0.45 (0.3-0.6)

Table 3: Bronchodilator response parameters at preschool-age for the detection of abnormal spirometry at school-age (N=89).

BDR: bronchodilator response, Δ%Pred: percentage change reported to predicted value, Δ%Init: percentage change reported to initial value, FEV1, FEV 0.75 and FEV 0.5 : forced expiratory volume in L during 1, 0.75 and 0.5 seconds of forced vital capacity, FEF25-75 : forced expiratory flow at 25–75% of the forced vital capacity in Ls, predicted: values according to Quanjer et al. (14), baseline: values calculated on the basis of the data from the present study, AUC : area under the curve, S : Sensitivity, E : Specificity, PPV : positive predictive value, NPV : negative predictive value, LR+ : Positive likelihood ratio, LR- : Negative likelihood ratio, CI : confidence Interval.

	Bronchodilator response at school age							
Preschool BDR	**Optimal Cut-off point**	**AUC (95% CI)**	**S (%) (95% CI)**	**E (%) (95% CI)**	**PPV (%) (95% CI)**	**NPV (%) (95% CI)**	**LR+ (95% CI)**	**LR- (95% CI)**
Δ%Pred FEV1	≥ 13%	0.59 (0.4-0.7)	35 (19-55)	88 (78-94)	50 (28-72)	79.5 (69-87)	2.9 (1.4-5.8)	0.74 (0.6-0.8)
Δ%Init FEV1	≥ 6.6%	0.6 (0.4-0.7)	61 (41-72)	61 (49-72)	35 (22-50)	82 (79-90)	1.5 (1.3-1.8)	0.64 (0.5-0.8)
Δ%Pred FEV0,75	≥ 12.3%	0.61 (0.5-0.8)	47.8 (47-91)	76 (64-84)	41 (25-59)	81 (69-89)	2 (1.4-2.7)	0.68 (0.6-0.8)
Δ%Init FEV0,75	≥ 9.3%	0.62 (0.5-0.8)	61 (41-78)	65.2 (53-76)	38 (24-54)	83 (70-91)	1.7 (1.5-2.1)	0.6 (0.5-0.8)
Δ%Init FEV0,5	≥ 23.4%	0.61 (0.5-0.8)	22 (10-42)	95.5 (87-98)	63 (31-86)	78 (68-85)	4.8 (0.6-38)	0.82 (0.7-0.9)
Δ%Pred FEF25-75	≥ 28%	0.56 (0.4-0.7)	39.1 (22-59)	76 (64-84)	36 (20-55)	78.1 (67-87)	1.6 (1-2.6)	0.8 (0.7-0.9)
Δ%Init FEF25-75	≥ 24.7%	0.57 (0.4-0.7)	61 (41-78)	58 (46-69)	33.3 (21-49)	81 (67-90)	1.4 (1.2-1.7)	0.68 (0.5-0.9)
Δ%Pred FEV1/ FVC	≥ 8.2%	0.61 (0.4-0.7)	30.4 (16-61)	88 (78-94)	47 (25-70)	78.4 (68-86)	2.5 (1-6)	0.8 (0.7-0.9)
Δ%Init FEV1/ FVC	≥ 9.3%	0.61 (0.4-0.7)	35 (19-55)	88 (78-94)	50 (28-72)	79.4 (69-87)	2.9 (1.4-5.8)	0.74 (0.6-0.8)
Δ%Pred FEV0,75/ FVC	≥ 9.6%	0.63 (0.5-0.8)	43.4 (26-63)	85 (74-92)	50 (30-70)	81.2 (70-89)	2.9 (1.8-4.5)	0.67 (0.6-0.8)
Δ%Init FEV0,75/ FVC	≥ 12.1%	0-64 (0.5-0.8)	39.1 (22-59)	89.4 (80-95)	56.3 (33-77)	81 (70-88)	3.7 (2-6.8)	0.68 (0.6-0.8)

Table 4: Bronchodilator response parameters at preschool-age for detection of bronchodilator response at school-age (N=89).

BDR: bronchodilator response, Δ%Pred: percentage change reported to predicted value, Δ%Init: percentage change reported to initial value, FEV1, FEV 0.75 and FEV 0.5 : forced expiratory volume in L during 1, 0.75 and 0.5 seconds of forced vital capacity, FEF25-75 : forced expiratory flow at 25–75% of the forced vital capacity in Ls, predicted: values according to Quanjer et al. (14), baseline: values calculated on the basis of the data from the present study, AUC : area under the curve, S : Sensitivity, E : Specificity, PPV : positive predictive value, NPV : negative predictive value, LR+ : Positive likelihood ratio, LR- : Negative likelihood ratio, CI : confidence Interval.

	Small Airway Dysfunction at school-age							
Preschool BDR	**Optimal Cut-off point**	**AUC (95% CI)**	**S (%) (95% CI)**	**E (%) (95% CI)**	**PPV (%) (95% CI)**	**NPV (%) (95% CI)**	**LR+ (95% CI)**	**LR- (95% CI)**
Δ%Pred FEV1	≥ 9.3%	0.69 (0.5-0.8)	62.5 (39-81)	75.3 (64-83)	35.7 (20-54)	90.2 (80-95)	2.5 (2-3)	0.5 (0.4-0.7)
Δ%Init FEV1	≥ 10.3%	0.72 (0.6-0.9)	62.5 (39-82)	76.7 (66-85)	37 (22-56)	90.3 (80-95)	2.7 (2.1-3.4)	0.49 (0.3-0.7)
Δ%Pred FEV0,75	≥ 18%	0.67 (0.5-0.8)	37.5 (18-61)	91.8 (83-96)	50 (25-75)	87 (78-93)	4.8 (2-11)	0.68 (0.6-0.8)
Δ%Init FEV0,75	≥ 9.3%	0.73 (0.6-0.9)	75 (51-90)	65.8 (54-96)	32.4 (20-49)	92.3 (82-97)	2.2 (1.9-2.5)	0.38 (0.2-0.6)
Δ%Init FEV0,5	≥ 22.6%	0.65 (0.5-0.8)	37.5 (18-61)	95.9 (88-98)	66-7 (35-88)	87.5 (79-93)	9.5 (2,8-30)	0.65 (0.5-0.8)
Δ%Pred FEF25-75	≥ 30.3%	0.57 (0.4-0.7)	18.8 (6.6-43)	67.1 (56-77)	11.1 (4-28)	79 (67-87)	0.57 (0.03-10)	1.1 (1-1.4)
Δ%Init FEF25-75	≥ 30.3%	0.59 (0.5-1)	56.3 (33-76)	67.2 (56-77)	27.3 (15-44)	87.5 (76-94)	1.7 (1.3-2.2)	0.65 (0.5-0.9)
Δ%Pred FEV1/FVC	≥ 6.2%	0.7 (0.5-0.8)	52.6 (32-73)	82.8 (72-90)	45.5 (27-65)	86.6 (76-93)	3.1 (2-4)	0.57 (0.5-0.7)
Δ%Init FEV1/FVC	≥ 7.3%	0.71 (0.6-0.9)	57.9 (36-77)	85.7 (76-92)	52.4 (32-72)	88.2 (78-94)	4.1 (2.9-5.6)	0.49 (0.3-0.6)
Δ%Pred FEV0,75/ FVC	≥ 7.6%	0.74 (0.6-0.9)	57.9 (36-77)	80 (69-88)	44 (27-63)	88 (77-94)	2.9 (2.2-3.8)	0.52 (0.4-0.7)
Δ%Init FEV0,75/ FVC	≥ 8.9%	0.76 (0.6-0.9)	63.2 (41-81)	81.4 (71-89)	48 (30-66)	89.1 (79-95)	3.4 (2.7-4.3)	0.45 (0.3-0.6)

Table 5: Bronchodilator response parameters at preschool-age for the detection of Small Airway Dysfunction at school-age (N=89).

BDR: bronchodilator response, Δ%Pred: percentage change reported to predicted value, Δ%Init: percentage change reported to initial value, FEV1, FEV 0.75 and FEV 0.5 : forced expiratory volume in L during 1, 0.75 and 0.5 seconds of forced vital capacity, FEF25-75 : forced expiratory flow at 25–75% of the forced vital capacity in Ls, predicted: values according to Quanjer et al. (14), baseline: values calculated on the basis of the data from the present study, AUC : area under the curve, S : Sensitivity, E : Specificity, PPV : positive predictive value, NPV : negative predictive value, LR+ : Positive likelihood ratio, LR- : Negative likelihood ratio, CI : confidence Interval

A retrospective study analyzed 1365 spirometry tests in asthmatic children. In said study, the BDR in FEV1 was compared with two different recommendations; ERS/ATS 2005, which recommends a BDR FEV1 ≥ 12% baseline value [25] vs ATS/ERS 2021, which recommends a BDR FEV1 > 10% of the predicted value (8). In this revision, it was discovered that the cut-off point over 10% to consider BDR in FEV1 can improv the diagnosis of asthma in children with a normal or nearly normal spirometry [26].

In the analysis of the preschool BDR with a positive SPT, most parameters improved the probability of abnormal spirometry but not SAD at school age. This could be related to two previous studies that reported that BDR has a weak to moderate correlation with allergic inflammation of the proximal airway as measured by bronchial nitric oxide, but null or weak correlation with alveolar nitric oxide, which measures allergic inflammation of the distal airway [27,28]. Strengths and limitations: One of the strengths of the study was the absence of loss to follow-up. Another point to highlight in this study is having included two methods to assess the BDR in preschoolers. Changes from predicted value are known to be independent of age and height, whereas changes from baseline may be height dependent, thus shorter children have less change in FEV1 after of the bronchodilator than the taller ones [29]. We can also highlight that the BDR was analyzed with spirometry parameters not often cited in the literature (FEV1/FVC and FEV 0.75/FCV) and they had a better performance than those usually used.

A study limitation was not being able to measure allergic sensitization with a SPT at school age due to the COVID 19 restrictions and quarantines that existed at the time of the second evaluation. Nor was asthma control measured to determine whether some of the BDR parameters could better identify uncontrolled asthma.

Interest in knowing the BDR in preschoolers with spirometry and other pulmonary function methods is becoming more prevalent by the day, however the methodological heterogeneity of the studies carried out so far does not allow for a universal recommendation. Although it is known that spirometry has less variability and better sensitivity than other studies to measure the BDR in preschoolers, (especially with FEV 0.75 and FEV 0.5.), more research is needed to recommend the most appropriate calculation methods and cut-off points for the diagnosis of asthma [30]. Important issues about BDR in children under 6 years of age remain to be investigated, such as its relationship with treatment response with inhaled corticosteroids, asthma control, and natural history of asthma, its genetics, and relationship with asthma phenotypes.

Conclusion

In conclusion, BDR is present in a significant number of asthmatic preschoolers. There are cut-off points in different preschool BDR spirometry parameters associated with the possibility of having abnormal spirometry, SAD or BDR at school age. These facts are important in assessing the severity of asthma and in making treatment decisions. Taken together, all these data suggest that lung function continues in

many cases from preschool age to school age. FEV 0.75/FVC and FEV 0.75 are important parameters in the evaluation of lung function and RBD in children under 6 years of age.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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